Functioning Paraganglioma and Gastrointestinal Stromal Tumor of the Jejunum in Three Women

Syndrome or Coincidence

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Abstract: Functioning paraganglioma and gastrointestinal stromal tumor (GIST) are uncommon tumors that occur mostly in a sporadic and isolated form, occasionally as components of multiple neoplasia syndromes, either separately or together. Separately, they occur in several inherited syndromes including multiple endocrine neoplasia 2, and the GIST, lentigines, and mast cell tumor syndrome. Together, they are variably prominent components of three syndromes: the familial paraganglioma and gastric GIST syndrome, neurofibromatosis type 1, and the Carney triad. The two former conditions are inherited as autosomal dominant traits; the latter does not appear to be inherited and affects young women predominantly. This article reports the nonfamilial occurrence of functioning paraganglioma and GIST of the jejunum in 3 women, 1 young (22 years) at initial presentation. The occurrences were unexpected because of the infrequency of the tumors. The neoplasms, respectively, did not show germline *SDHA*, *SDHB*, *SDHC*, and *SDHD,* and *KIT* mutations associated with familial paraganglioma and familial GIST. The paraganglioma-jejunal GIST combination may be the harbinger of a rare genetic syndrome, a variant of the Carney triad or the paraganglioma-gastric stromal sarcoma syndrome, or be coincidental.

Key Words: paraganglioma, GIST, jejunum, multiple neoplasia syndrome, Carney triad, genetics

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Paragangliomas are uncommon tumors that arise from the chromaffin cells of the adrenal medulla (pheochromocytoma) and the extra-adrenal paraganglionic system (extra-adrenal paraganglioma). The extra-adrenal tumors are usually asymptomatic and become manifest as a painless mass or are found incidentally. A minority causes symptoms due to secretion of excessive amounts of catecholamines. Most paragangliomas occur as sporadic and isolated events, but about 10% are familial,[16,18] occurring alone or with a variety of other neoplasms constituting multitumor syndromes (Table 1). The familial paraganglioma syndromes are caused by germline mutations in *SDHB*, *SDHC*, and *SDHD* genes.[2]

Gastrointestinal stromal tumors (GISTs) are uncommon mesenchymal neoplasms of the alimentary tract. Two thirds occur in the stomach[20]; about one fourth develops in the small intestine, usually in the duodenum.[8] In the past, these tumors were considered to be of smooth muscle origin because of their light microscopic appearance and intramural location within the bowel wall. This interpretation has now largely been abandoned because immunocytochemical and electron microscopic studies, respectively, failed to show the smooth muscle antigens (actin and desmin) and structures (continuous basement membrane material, many pinocytotic vesicles, dense bodies, and organized filaments) that are present in myomatous tumors elsewhere in the body, in the uterus, for example.[7] Instead, the immunocytochemical studies showed KIT (CD117) and CD34 immunopositivity, attributes that are restricted in the gut to the interstitial cells of Cajal.[26] The interstitial cells of Cajal are mesodermal derivatives that become associated with the autonomic myenteric plexus during development and are thought to regulate peristalsis.[28,29]

Today, the majority of alimentary tract intramural tumors are interpreted as GISTs, including tumors formerly referred to as gastrointestinal autonomic nerve (GAN) tumor and plexosarcoma.[10,15] Activating mutations of the *KIT* gene are often found in GISTs.[11,12] GISTs are not a homogeneous group of neoplasms, however. Immunocytochemically, some show differentiation toward smooth muscle, others toward nerve, some toward histiocytes, a small group toward smooth muscle and nerve, and another small group shows no differentiation.[11,13,22] GISTs also show strong site-dependent genetic heterogeneity.[9] The tumor is a major or minor component of certain rare syndromes, familial and nonfamilial (Table 1).

This article describes the occurrence of functioning abdominal paraganglioma and GIST of the jejunum in each of 3 women, none of whom had a family history of either neoplasm. Because of the rarity of each of the neoplasms, finding the combination in 3 patients merits attention. The combination could represent a new syndrome, be a variant form of the

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TABLE 1. Syndromes Including Paraganglioma or GIST or Both

Syndrome	Locus Name	Gene Locus	Inheritance	Gene	Reference
Familial paraganglioma	PGL 1	11q23	AD	*SDHD*	1
Familial paraganglioma	PGL 2	11q13.1	AD	*SDHC*	17
Familial paraganglioma	PGL 3	1q22-23	AD	*SDHB*	23
MEN 2A and MEN 2B		10q11.2	AD	*RET*	21
von Hippel-Lindau disease	VHL	3p26 25,11q13	AD	*VHL*	14
Familial GIST	Unknown	Unknown	AD	*KIT* (JM domain)	24
GIST, lentigines, urticaria pigmentosa, mast cell tumors	Unknown	Unknown	AD	*KIT* (JM domain)	3,24,25
GIST and dysphagia	Unknown	Unknown	AD	*KIT* (TK-11 domain)	12
Paraganglioma-GIST	Unknown	Unknown	AD	Unknown	6
Carney triad	Unknown	Unknown	Sporadic	Unknown	5
Neurofibromatosis type 1	NF1	17q11.2	AD	*NF1*	27

GIST, gastrointestinal stromal tumor; AD, autosomal dominant; SDH, succinate dehydrogenase; MEN, multiple endocrine neoplasia.

Carney triad or of the paraganglioma-gastric stromal sarcoma syndrome, or be happenstance.

CASE REPORTS

The study was carried out with approval from the Institutional Review Boards of Mayo Rochester (IRB protocol no. 826-04) and the National Institute of Child Health and Development (IRB protocol no. OOCH180).

Case No. 1

A 57-year-old woman attended the Mayo Clinic in 2000. She had a 5-year history of spells (pressure sensation in the upper chest, forceful heartbeat, a lump in the throat, and sensation of blood rushing to her head) associated with hypertension and, latterly, the development of type 2 diabetes. Investigations at the home hospital had revealed elevated urinary levels of metanephrines. Abdominal computed tomography (CT) and magnetic resonance imaging showed a 3.2 × 2.2 cm upper abdominal mass between the inferior vena cava and aorta. The adrenal glands were normal. Indium (In-III)-labeled octreotide scintigraphy demonstrated a small focus of uptake close to the right adrenal gland that was consistent with a functioning paraganglioma. Hypertension and spells were controlled with α- and β-adrenergic blockade at abdominal exploration. The para-aortic mass was excised together with the adrenal gland, which was intimately associated with it. Microscopically, the mass was a paraganglioma. Postoperatively, fractionated plasma metanephrines normalized.

In 2003, the patient presented again at her home hospital with anemia (hemoglobin level fell to 6.4 g/dL) and melena. Exhaustive gastrointestinal investigations, including upper endoscopy, colonoscopy, and small bowel imaging, gave normal results. Capsule endoscopy showed arteriovenous malformations at 30, 92, and 94 minutes. Mesenteric angiography revealed 1) a small bowel lesion (Fig. 1) with abnormal contrast opacification and arteriovenous shunting; 2) aneurysmal dilatation of the left gastric artery to 4 times its normal diameter, small dilatations of the splenic artery, and the proximal common hepatic artery; and 3) focal areas of increased and decreased diameter of mid-jejunal artery branches, possibly small arteriovenous malformations. A technetium scan demonstrated a small vascular nodule, most likely a tumor in the mid-jejunum. The lesion was embolized with a small volume of 250 to 350 μm Ivalon particles and the intestinal bleeding was stopped. The patient returned to the Mayo Clinic, and a laparotomy was performed because of concern that the tumor, although small, might be malignant. The lesion was removed by a segmental resection of the jejunum. Microscopically, it was a GIST (Fig. 2). The patient is currently well at the age of 61 years. There was no family history of paraganglioma or GIST.

Case No. 2

In 1969, a 22-year-old patient, then 7 months pregnant, was found to have marked hypertension. A right adrenalectomy was performed for a pheochromocytoma; an adjacent large "lymph node" was also excised. The latter was interpreted as possibly metastatic pheochromocytoma. The lesion likely was an extra-adrenal paraganglioma (see Results).

In 1991, at age 45 years, the patient complained of palpitations and was found to be hypertensive again. Details of the investigation at this time are no longer available. However, a contralateral adrenalectomy was performed for pheochromocytoma. At surgery, a small bowel tumor was discovered incidentally and resected. This was

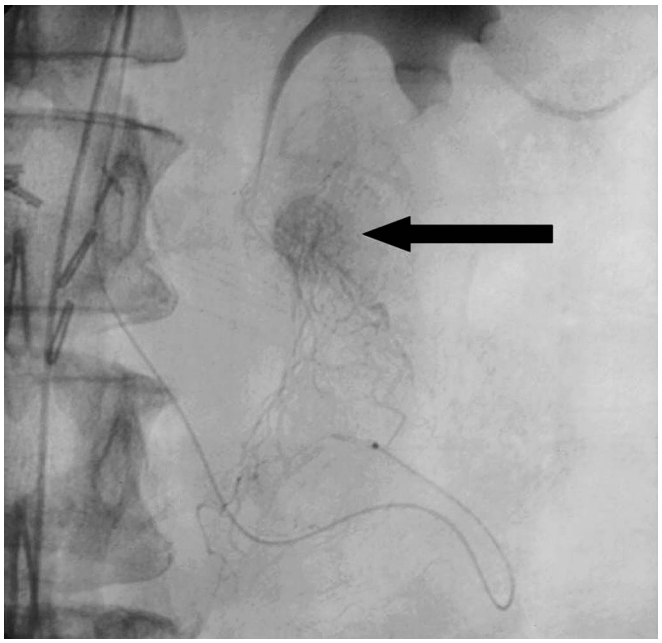

FIGURE 1. Selective mesenteric angiography (case no. 1). The jejunal tumor (arrow) is visible just below the renal pelvis.

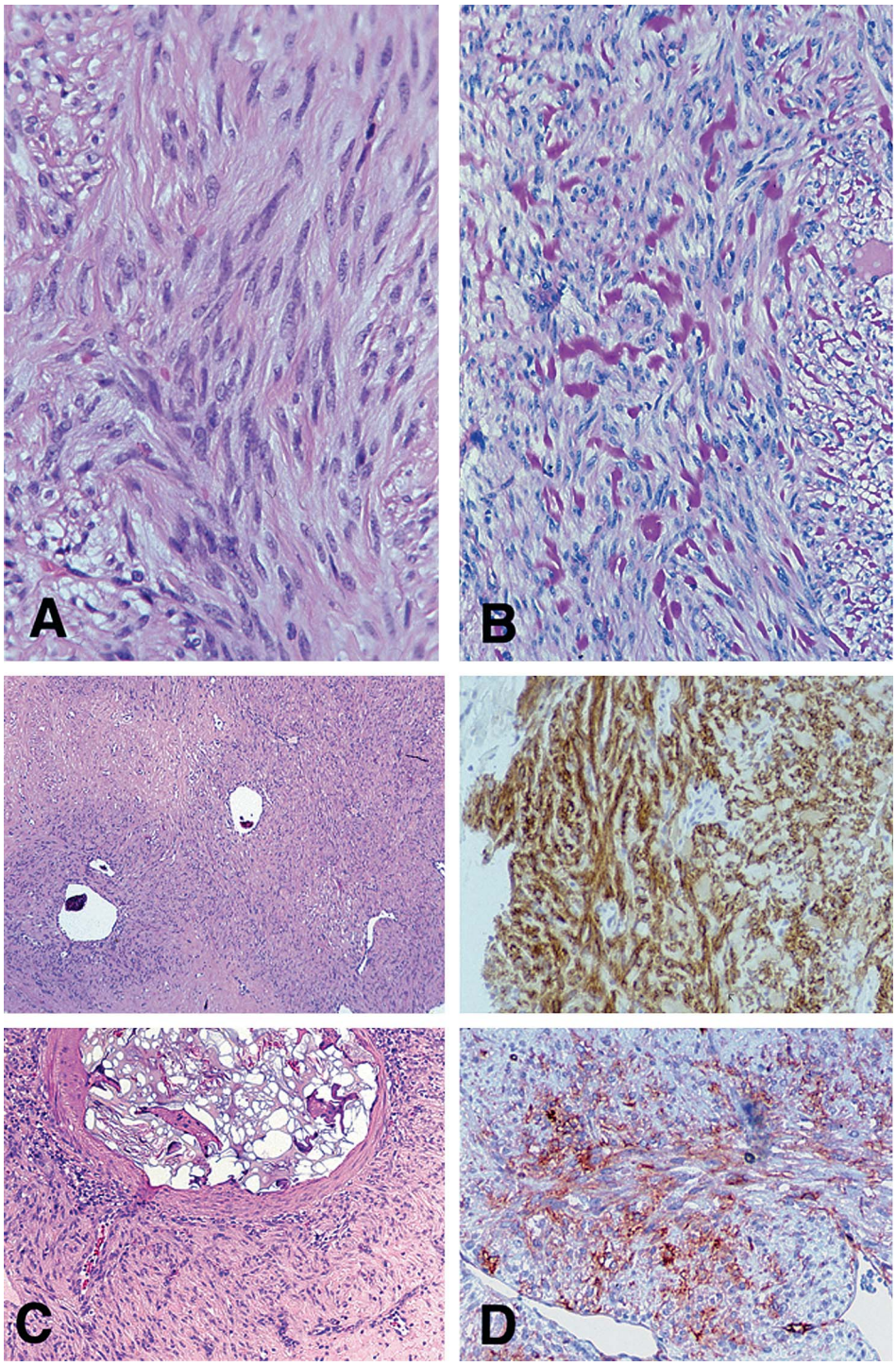

FIGURE 2. Jejunal GIST (case no. 1). A, Fascicle of cells cut longitudinally shows uniform plump nuclei with blunt ends and barely perceptible nucleoli. B, Irregularly shaped broad strands of intercellular PAS-positive skenoid fibers. C, Top, Dilated blood vessels and zones of fibrosis. Bottom, Foreign material consistent with microcoil material and associated foreign-body giant cells plug a large intratumoral blood vessel. D, The tumor cells were immunoreactive for KIT (top) and CD34 (bottom).

interpreted as GAN. Postoperatively, the blood pressure returned to normal.

In December 1992, a pelvic sonogram showed a right "ovarian mass." Laparotomy was performed, and pelvic and peritoneal metastatic GAN tumor was found (Fig. 3). Six courses of chemotherapy (adriamycin, carboplatin, dacarbazine, and mitomycin) were administered. Abdominal CT examination in April 1994 showed miliary peritoneal implants and a 5-cm mass in the liver. The patient was referred to Mayo Clinic. Additional chemotherapy with ifosfamide and etoposide was prescribed but proved ineffective. The patient died in October 1995.

Case No. 3

The patient, now 66 years of age, was found to have hypertension at the age of 39 years when donating blood. She was treated with a variety of antihypertensive regimens. At the age of 63 years, she developed hypertensive encephalopathy. The urinary excretion of norepinephrine, normetanephrine, total catecholamines, and total

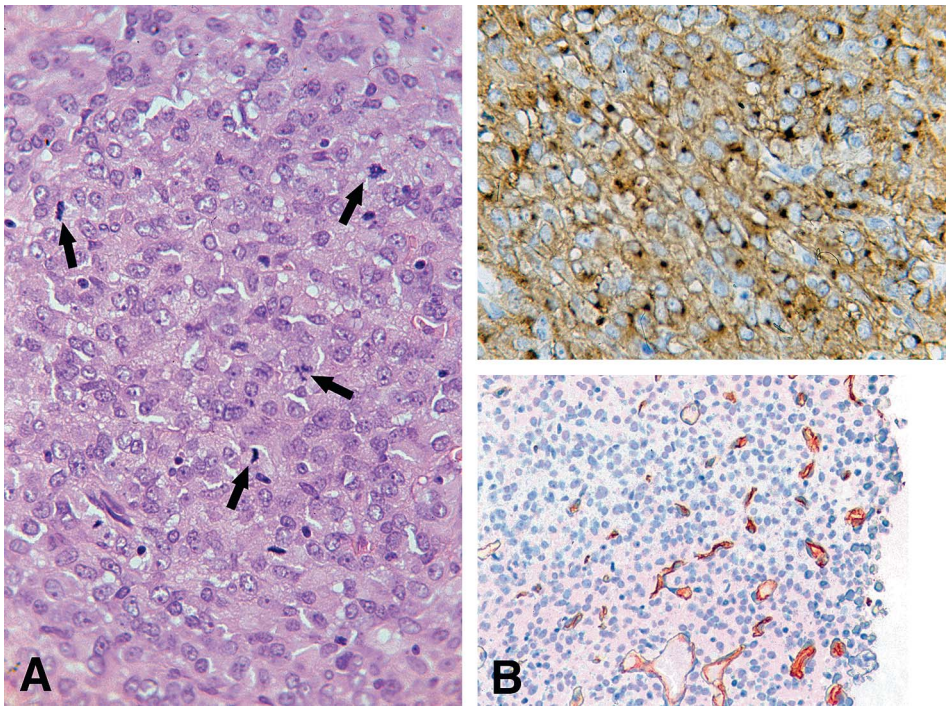

FIGURE 3. Metastatic GIST (case no. 2). A, Sheet of poorly outlined cells with round nuclei and small nucleoli. Multiple mitotic figures are present (arrows). B, The tumor cells stained strongly for KIT (top) and did not react to CD34 (blood vessels are positive).

metanephrines was increased five- to tenfold above normal. A CT revealed a right-sided extra-adrenal mass and bilateral adrenal enlargement. Meta-iodobenzylguanidine ^{131}I scan showed abnormal uptake adjacent to the right upper abdominal aorta consistent with the periaortic mass seen on CT examination. Bilateral adrenalectomy was performed (Fig. 4) and the extra-adrenal mass, a paraganglioma, was excised. A very hard mass was found incidentally in the mid-jejunum (Fig. 4). This was also resected and proved to be a GIST. Later, a 300-mg right superior parathyroid adenoma was excised. The patient is presently well. A younger sister reportedly has a history of hypertension and hyperparathyroidism.

METHODS

The available medical reports, histologic slides, tumor blocks, and pathology reports were obtained in the 3 cases. Slides and paraffin blocks from the 1969 pheochromocytoma and the small bowel primary in case no. 2 had been discarded; those from the patient's metastases were obtained.

Light Microscopy and Immunohistochemical Methods

Five-micron-thick sections made from formalin-fixed, paraffin-embedded tumor blocks were stained using the hematoxylin and eosin and periodic acid–Schiff methods. Immunohistochemical staining was performed on similar sections with use of the streptavidin-biotin-peroxidase complex method and antibodies listed in Table 2.

Fluorescent In Situ Hybridization (FISH)

To detect potential anomalies of the *PDGFRA* and *KIT* genes located in the 4q11 chromosome region, direct labeled breakapart FISH probes were designed from bacterial artificial chromosomes (BACs). BACs flanking each gene region of interest were selected and validated according to standard methods.[26] Centromeric to the *PDGFRA* gene, clones were selected to create a probe of 521 kb and clones telomeric were selected to create a probe of 661 kb. Centromeric to the *c-KIT* gene, clones were selected to create a 400-kb probe and telomeric clones were selected to create a probe of 460 kb. The search for BACs on 4q11 for both *PDGFRA* and *c-KIT* was accomplished using the UCSC (University of California Santa Cruz) Genome Browser (http:Hwww.USC.edu) and the National Center for Biotechnology Information (NCBI) website (http:www.ncbi.nlm.nih.gov/).

FISH slides consisted of 5-μm sections cut from the paraffin-embedded tumor specimens and mounted on glass slides. The slides were subjected to standard FISH pretreatment, hybridization, and fluorescence microscopy methods.[4] Representative interphase FISH images were captured and digitized.

Analysis of Sequence Variation Among KIT- and Pheochromocytoma-Associated Genes

Genomic DNA was extracted from formalin-fixed, paraffin-embedded blocks of the paragangliomas (2 cases) and the GISTS (3 cases, one tumor a metastasis) utilizing a standard extraction protocol and the Qiagen DNA Extraction Kit (Qiagen, Valencia, CA). Mutation analysis for all exons, exon-intron boundaries, and flanking intronic regions was performed for *SDHA, SDHB, SDHC*, and *SDHD* and *KIT*. PCR was performed using Qiagen HotStarTaq kit for 38 cycles with a 55°C annealing temperature for all primers for all four genes. An aliquot of the PCR product was purified using Exonuclease I/shrimp alkaline phosphatase treatment (New England Biolabs, Beverly, MA; USB Corporation, Cleveland, OH). The purified amplicons were directly sequenced using BigDye Terminator v. 20 Cycle Sequencing Kit (Applied Biosystems, Foster City, CA) and analyzed on an ABI 3730

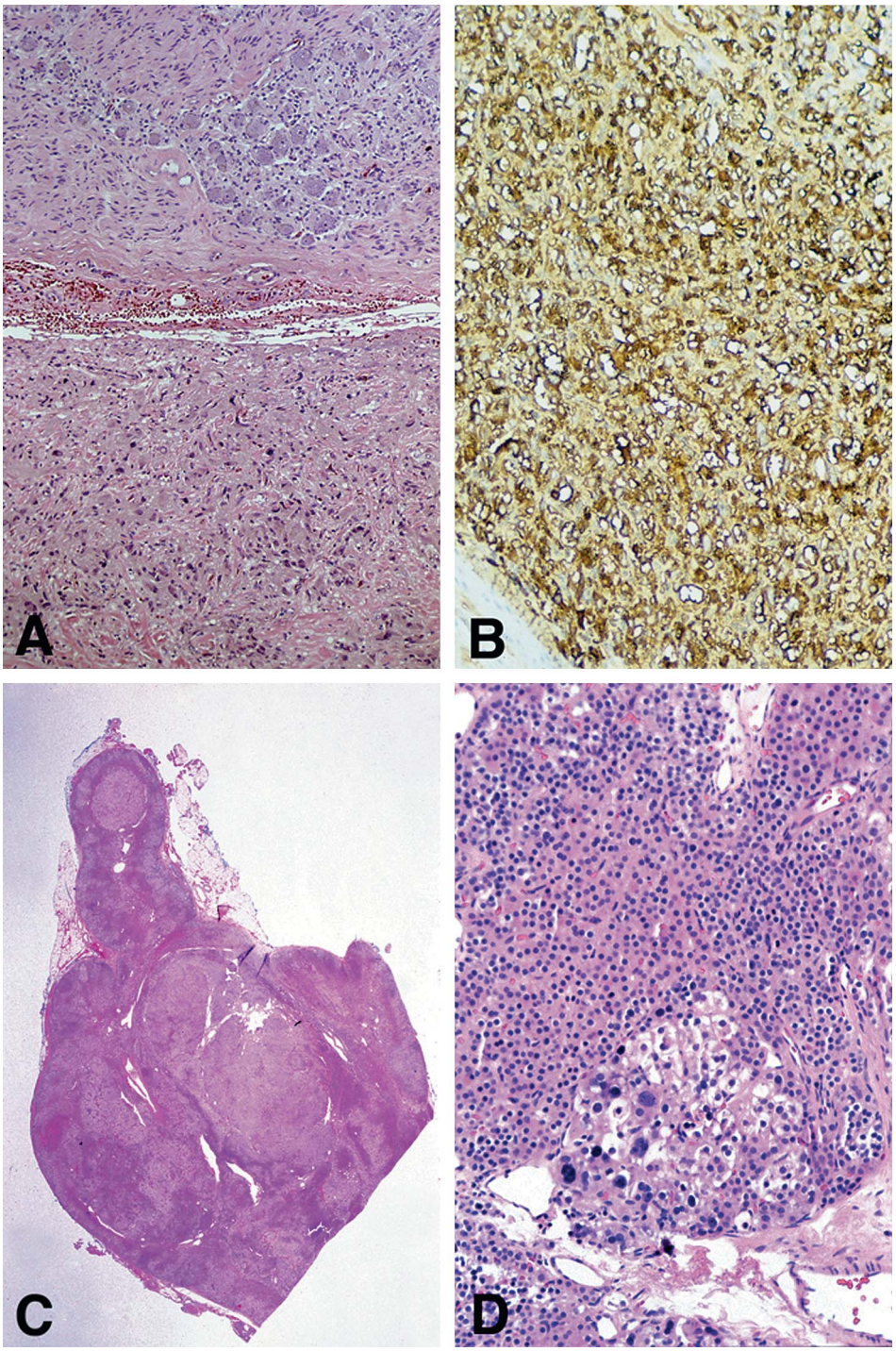

FIGURE 4. Paraganglioma, nodular adrenal cortical hyperplasia, and parathyroid adenoma (case no. 3). A, The paraganglioma was in close proximity to an aorto-sympathetic ganglion. B, Paraganglioma cells were positive for chromogranin. C, The adrenal gland was expanded by several nodules of cortical cells and zones of diffuse cortical hyperplasia. D, The parathyroid adenoma featured medium-sized and small cells with uniform hyperchromatic nuclei and eosinophilic cytoplasm. There was a focus of cells with the large degenerating nuclei commonly observed in parathyroid adenoma.

DNA Analyzer (Applied Biosystems). PCR primers used for the *KIT* and *SDHA*, *SDHB*, *SDHC*, and *SDHD* analyses were described previously.[19,25]

Search of Mayo Clinic and Literature Databases

A computer search was done of Mayo Clinic records from 1975 through 2002, and the world literature from 1975 through 2004 for cases featuring paraganglioma or pheochromocytoma or both, and small intestinal GIST, leiomyoma, leiomyosarcoma, neurofibroma, neurofibrosarcoma, and plexosarcoma.

RESULTS

Clinical

The patients were 3 unrelated women. They ranged in age from 22 to 52 years at onset of symptoms of functioning

TABLE 2. Antibodies Used for Immunocytochemical Studies, Sources, and Methods

Antibody	Source	Dilution	Clone	Pretreatment
c-KIT	Santa Cruz Tech Santa Cruz, CA	1:600	Polyclonal	EDTA, Techmate
CD34	Becton Dickinson San Jose, CA	1:50	My10	EDTA, Techmate
PDGFRA	Santa Cruz Tech Santa Cruz, CA	1:50	Polyclonal	EDTA, Dako Autostainer
Vimentin	Dako Carpinteria, CA	1:500	Polyclonal	Protease 2, Ventana ES
Actin	Dako Carpinteria, CA	1:50	HHF35	Protease 2, Ventana ES
Desmin	Dako Carpinteria, CA	1:100	DER11	Protease 2, Ventana ES
Neurofilament	Dako Carpinteria, CA	1:75	2F11	Protease 2, Ventana ES
S-100	Dako Carpinteria, CA	1:800	MC-1	44% formic acid, Ventana ES
Chromogranin A	Roche Indianapolis, IN	1:1000	LK2H10	EDTA, Dako Autostainer
ACTH	Novocastra Burlingame, CA	1:300	NCL-ACTH	None

paraganglioma. Excision of the tumors restored the urinary catecholamine excretion to normal levels, permanently in 2 patients and for 21 years in the third who at that time developed a new and presumably independent paraganglioma. None of the tumors recurred locally or metastasized.

The patients ranged in age from 45 to 66 years at discovery of their jejunal GIST. Two of the GISTs were found incidentally (during the operation for paraganglioma). The third tumor (in case no. 1) became ulcerated and bled resulting in melena and anemia. Imaging techniques in the case revealed a small intestinal tumor and also a series of vascular anomalies (Fig. 1). The three tumors were treated by segmental resection of the small intestine. The tumor did not recur or metastasize in 2 patients (follow-up, 12 and 18 months, respectively). The third patient (case no. 2) developed disseminated intra-abdominal metastases that were unresponsive to chemotherapy and proved fatal. Selected features of the tumors and other findings in the patients are presented in Tables 3 and 4. Serum calcium was normal in case nos. 1 and 2 and elevated in case no. 3. None of the patients had a family history of paraganglioma, GIST, or neurofibromatosis.

Pathology

The paragangliomas ranged in size from 3.5 cm in diameter to 4.2 × 3.5 × 2.6 cm. All were typical microscopically (Fig. 4) and stained for chromogranin. The retroperitoneal lymph node excised in case no. 2 measured 7 × 5.5 × 5 cm and weighed 53 g. Histologically, it showed paraganglioma tissue and no lymphoid tissue. The absence of lymphoid tissue and the subsequent behavior of the lesion (no recurrence) suggests that the "lymph node" likely was an extra-adrenal paraganglioma rather than a lymph node metastatically involved by pheochromocytoma, as was suggested in the original pathology report. Autonomic ganglion and nerve were intimately related to the paraganglioma capsule in case nos. 2 and 3 indicating that the tumors had arisen close to the aortosympathetic chain. There was bilateral nodular and diffuse adrenocortical hyperplasia (total adrenal weight was 23 g) in case no. 3 (Fig. 4) that did not cause symptoms of adrenocortical hyperfunction. Because the patient's paraganglioma did not stain for ACTH, ectopic secretion of ACTH was not the cause of the adrenal cortical abnormality. The patient was also found to have a parathyroid adenoma that weighed 300 mg

TABLE 3. Selected Clinical and Pathologic Features of the Tumors in Three Women

	Abdominal Paraganglioma			Jejunal GIST		
Case No.	Age at Presentation	Extraadrenal	Adrenal	Age at Presentation (yr)	Metastasis	Other
1	57	+		60	No	Mesenteric artery aneurysms and arteriovenous malformations
2	22	+	+, bilateral	45	Yes	None
3	63	+		63	No	Bilateral adrenocortical hyperplasia, parathyroid adenoma

+, present.

TABLE 4. Pathologic Features of Jejunal GISTs

	Case No. 1	Case No. 2	Case No. 3
Size (cm)	1.2 × 1.2 × 1.7	6 × 5.3 × 3.5	1.3 × 1 × 0.8
Gross appearance	Well-circumscribed nodule	Yellow gray tumor penetrating through wall to serosa	Ovoid, tan, glistening tumor
Location in bowel wall	Submucosa	Transmural with serosal involvement	Muscularis propria
Ulceration	Yes	Yes	No
Periphery	Circumscribed, unencapsulated	(Slides available from metastasis only)	Circumscribed, unencapsulated
Cellularity	Moderate	High	Moderate
Cell type	Spindle	Epithelioid and spindle	Spindle
Nuclei	Regular, cigar-shaped with small nucleoli; no mitoses	Regular, round and oval; many mitoses including atypical types	Regular, cigar-shaped with small nucleoli; no mitoses
Other	PAS-positive skenoid fibers, dilated sinusoids, fibrotic zones	None	PAS-positive confluent skenoid fibers, dilated sinusoids
KIT	Membranous positivity	Punctate and membranous positivity	Membranous and punctate positivity
CD34	Patchy weak membranous and diffuse cytoplasmic positivity	Negative	Membranous positivity
Vimentin	Positive	Positive	Positive
PDGFRA, actin, desmin, S-100, neurofilament, chromogranin	Negative	Negative	Negative
Metastasis	No	Yes (peritoneum, ovaries, and liver)	No

(Fig. 4). Features of the GISTs are summarized in Table 4, and their microscopic appearance illustrated in Figures 2 and 3.

FISH and Molecular Analysis

No break apart, deletion, or duplication of the *PDGFRA* and *KIT* genes located in the 4q11 chromosome region were detected. No *SDHB*, *SDHC*, *SDHD SDHA*, *KIT*, or *PDGFRA* gene mutations were detected.

Search of Mayo Clinic and Literature Databases

No additional cases of the paraganglioma-small intestinal GIST combination in patients with a normal phenotype were found.

DISCUSSION

This report concerns the occurrence of paraganglioma and GIST of the jejunum in 3 unrelated patients, all women. The paragangliomas were typical by light microscopy and were strongly chromogranin A positive. The jejunal tumors were histologically consistent with GISTs and were KIT (3 of 3) and CD34 (2 of 3) positive immunocytochemically. Unusual features of the paragangliomas were 1) bilaterality and multicentricity (1 patient) and 2) young age at first occurrence (22 years) (1 patient). Unusual features of the GISTs were 1) their jejunal location, 2) absence of either smooth muscle or neural markers, and 3) absence of the *KIT* and *PDGFRA* gene mutations associated with sporadic and familial forms of the neoplasm.

These unusual features indicate that both tumors differed from their usual sporadic counterparts and for this reason raised suspicion that there might be an etiologic link between them. A connection in the context of a syndrome is very plausible because there are several already established such connections between the two neoplasms (Table 1). It is tempting to relate the paraganglioma-jejunal GIST combination to the syndrome known as the Carney triad because the combination does not appear to be familial and appears to have a female predilection. However, GISTs in the Carney triad have occurred only in the stomach (with only minimal involvement of the proximal duodenum in a few cases) and the paraganglioma in this disorder is almost always extra-adrenal. Furthermore, none of the 3 patients had radiologic evidence of pulmonary chondroma, the second commonest component of the Carney triad. It is of course possible that the 2 surviving patients, now aged 61 and 66 years, might still develop pulmonary chondroma(s).

The paraganglioma-jejunal GIST association could also be a variant of the paraganglioma-gastric stromal sarcoma syndrome (Table 1). This is unlikely, however, because small intestinal GISTs are not simply small intestinal counterparts of the gastric tumor; the 2 tumors have been demonstrated to be cytogenetically different.[31] It is also unlikely that they were associated with neurofibromatosis because of the age of the patients and lack of other manifestations of the disorder.

The additional conditions in the patients deserve comment. The significance of the vascular anomalies in our case no. 1 is unknown; angiographic studies were not done in the other 2 patients; there was no clinical indication. There is a single case report of jejunal GIST associated with an angiodysplasia.[30] The latter anomaly, however, was part of the tumor and not apart from it, as were the multiple vascular anomalies in our case no. 1. The bilateral adrenocortical hyperplasia in case no. 3 is reminiscent of the unilateral or bilateral adrenocortical adenoma(s) that have occurred in 10% of patients with the Carney triad.[5] The adrenal cortex, however, was normal in case no. 1, and there was no mention of a cortical abnormality in the pathology report in case no. 2. The patient with the adrenal cortical abnormality also had parathyroid adenoma, a tumor that has occurred in 2 of 101 patients with the Carney triad.

In summary, we present the cases of 3 unrelated women, each with functioning paraganglioma and GIST of the jejunum and no family history of either neoplasm. Both tumors had features that set them apart from their sporadic counterparts. The paraganglioma-jejunal GIST combination may be the harbinger of a new syndrome, be a variant of the Carney triad or the paraganglioma and gastric stromal sarcoma syndrome, or be happenstance. Identification of additional cases of the tumor combination and further advances in molecular genetics may provide an explanation of the events.

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